

Remarks

The March 10, 2003 Official Action has been carefully reviewed. In view of the amendments submitted herewith and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the March 10, 2003 Official Action. The initial due date for response, therefore, was June 10, 2003. A petition for a 2 month extension of the response period is presented with this response, which is being filed within the one month extension period.

In the March 10, 2003 Official Action, the Examiner notes that claim 95 is in condition for allowance.

The Examiner has rejected claims 89 as allegedly failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph.

Claims 78-94 also stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner's reasons in support of this ground of rejection are set forth at pages 3 and 4 of the March 10, 2003 Official Action.

The Examiner has also rejected claims 78-80, 82-88, 90, and 93 under 35 U.S.C. §102 as allegedly anticipated by U.S. Patent No. 6,410,255. Claims 78, 79, 82-88, 90, and 93 also stand rejected under 35 U.S.C. §102 as allegedly anticipated by U.S. Patent No. 5,795,729. Additionally, the Examiner has rejected claims 78-88 and 90-93 under 35 U.S.C. §103 as allegedly unpatentable over U.S. Patent Nos. 6,410,255 and 5,795,729 in view of Haugland ("Handbook of Fluorescent Probes and Chemicals, 5th Edition" (1992) Molecular Probes, pp. 90-93). The Examiner's reasons in support of this ground of rejection are set forth at pages 4-6 of the March 10, 2003 Official Action.

The foregoing rejections constitute all of the grounds set forth in the March 10, 2003 Official Action for refusing the present application.

The Examiner has also made of record an additional prior art reference which is deemed by the Examiner to be pertinent to the Applicants' disclosure. Specifically, U.S. Patent No. 6,376,257 to Perechini has been made of record, but no rejection has been made based on this reference.

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

**CLAIM 89 AS AMENDED MEETS THE WRITTEN DESCRIPTION REQUIREMENT
OF 35 U.S.C. 112, FIRST PARAGRAPH**

The Examiner has rejected claim 89 under 35 U.S.C. 112, first paragraph as allegedly containing matter which was not described in the specification as to convey to a skilled artisan that the inventors had possession of the claimed invention. Specifically, the Examiner indicates that claim 89 recites an enzyme that is recombinantly produced whereas the specification discloses the peptide substrates as recombinant polypeptides. Applicants have accordingly amended claim 89 to recite a peptide substrate which is recombinantly produced, thereby obviating the Examiner's rejection of claim 89 under 35 U.S.C. §112, first paragraph.

**CLAIM 78 AS AMENDED AND CLAIMS 79-94 FULLY SATISFY THE
REQUIREMENTS OF 35 U.S.C. 112, SECOND PARAGRAPH**

In support of the 35 U.S.C. §112, second paragraph rejection of claims 78-94 the Examiner asserts that claim 78 is vague and indefinite for the recitation of the phrase "functional fragments thereof." Specifically, the Examiner indicates the inclusion of the phrase is considered redundant, inasmuch as functional fragments are peptide substrates in

accordance with the scope of the claim. Applicants have, therefore, removed the phrase from claim 78 thereby rendering moot the Examiner's rejection of this claim.

The Examiner also contends that claim 78 is confusing for the recitation of the phrase "otherwise intact." Applicants disagree with the Examiner's assessment. Specifically, the Examiner contends that "intact" means unchanged and is therefore unsure as to how a modified peptide can be intact at the same time. Applicants respectfully point out that intact, according to the Merriam-Webster dictionary, means entire or "having no relevant component removed or destroyed." Applicants have, however, amended claim 1 to remove the phrase "otherwise intact" which the Examiner perceives as confusing. Applicants submit that claim 78, as amended, still connotes that the composition is not hydrolyzed by a protease into more than one fragment, as the unmodified state and modified states are stated to possess a first and second structural conformation wherein the proximity sensors are spaced apart at characteristic distances. By removal of the phrase, which may be viewed as redundant in view of the additional recitation just noted, Applicants have overcome the Examiner's rejection of claim 78 under 35 U.S.C. §112, second paragraph.

The Examiner has also rejected claim 82 under 35 U.S.C. §112, second paragraph as allegedly confusing for the recitation of the term "post-translational." Specifically, the Examiner contends that post-translational modifications can only be performed on a peptide that has been translated from mRNA. Applicants strenuously disagree with the Examiner's position and submit that the phrase post-translational modification would be interpreted by a skilled artisan to encompass the in vitro modification of a chemically synthesized peptide. Indeed, posttranslational modification is defined in Molecular Biology of the Cell (Alberts, B. et al., Eds.; 3rd Edition, 1994, Garland Publishing, New York,

page G-19) as an "enzyme-catalyzed change to a protein made after it is synthesized." No requirement of being "translated" from mRNA is made.

In view of the amendments presented herewith and the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 78-94 under 35 U.S.C. §112, second paragraph.

**CLAIM 78 AS AMENDED AND CLAIMS 79-80, 82-88, 90, AND 93 ARE
NOT ANTICIPATED BY US PATENT NO. 6,410,255**

A rejection under §102 is warranted only when the cited reference identically discloses the subject matter of the invention as claimed. In re Bond, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Applicants respectfully submit that the rejection of claims 78-70, 82-88, 90, and 93 under §102 is not warranted in this case because U.S. Patent 6,410,255 to Pollok et al. (hereinafter Pollok) does not identically disclose the claimed invention.

The Examiner contends that Pollok discloses FRET peptides that can be used to monitor posttranslational modification activity. A review of Pollock reveals, however, that the presence of a posttranslational modification is monitored by cleavage of a probe by a protease. Specifically, at column 3, lines 34 through 45, the substrate which contains the fluorescent probes also contains "recognition motif for a posttranslational type activity and a protease site," wherein "modification at the recognition motif alters protease activity at the protease site." Additionally at column 5, lines 40 through 44, Pollok recites that "in the present invention, post-translational modification of a polypeptide results in the modulation of the rate and efficiency of cleavage of the modified polypeptide compared to the non-modified peptide." The instant invention, as claimed in amended claim 78, does not require protease activity to monitor post-translational modifications, but rather allows

for the monitoring of enzyme activity through conformational changes in the substrate structure. Indeed, amended claim 78 recites that the peptide possesses "a first structural conformation in said unmodified state" and "a second structural conformation in said modified state." Pollok does not speak to conformational changes of the substrate and relies solely on the modification of the "rate at which a protease cleaves the polypeptide" to monitor enzymatic activity (see abstract). Because Pollok fails to identically disclose the subject matter of the claimed invention, Applicants respectfully submit that the rejection of claims 78-80, 82-88, 90, and 93 under 35 U.S.C. §102(a) based on Pollok is improper and should, therefore, be withdrawn.

**CLAIM 78 AS AMENDED AND CLAIMS 79, 82-88, 90, AND 93 ARE NOT
ANTICIPATED BY US PATENT NO. 5,795,729**

As noted hereinabove, a rejection under §102 is warranted only when the cited reference identically discloses the subject matter of the invention as claimed. In re Bond, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Applicants respectfully submit that the rejection of claims 78, 79, 82-88, 90, and 93 under §102 is not warranted in this case because U.S. Patent 5,795,729 to Lee et al. (hereinafter Lee) does not identically disclose their invention.

The Examiner contends that Lee discloses enzyme substrates containing reporter and quencher fluorescent probe molecules connected by a suitable linker. A careful review of Lee, however, reveals that Lee discloses that the quencher molecule itself is modified by a reagent to "a second state which has a reduced ability to quench the reporter molecule" (see the abstract and column 4, lines 45 through 62). This conversion of the quencher to a second state may involve hydrolysis, peptide bond cleavage, phosphate bond cleavage, oxidation, or reduction" (column 4 line 66 through column 5, line 2). Notably, a conformational change between the

fluorescent probe and the quencher is not disclosed or suggested. Applicants further submit that the instant invention is not limited to substrates containing a quencher molecule that is chemically altered by a reagent (i.e. enzyme) from a state that can quench a fluorescent probe to a state that can only quench the fluorescent probe to a lesser extent. Indeed, the instant invention as claimed in amended claim 78 comprises a peptide substrate of the modifying enzyme and proximity sensor-peptides. In contrast to Lee, the peptide substrate, and not the proximity sensor peptides (e.g. fluorescent probes), of the instant invention are chemically modified by the enzyme. Because Lee fails to identically disclose the subject matter of claims 78, 79, 82-88, 90, and 93, the rejection of these claims under 35 U.S.C. §102 based on Lee is untenable and should, therefore, be withdrawn.

**CLAIM 78 AS AMENDED AND CLAIMS 79-88 AND 90-93 ARE NOT
RENDERED OBVIOUS BY U.S. PATENT NOS: 6,410,255 AND 5,795,729
CONSIDERED IN VIEW OF HAUGLAND (1992)**

The Examiner has rejected claims 78-88 and 90-93 under 35 U.S.C. §103(a) as unpatentable over Pollok and Lee in view of Haugland ("Handbook of Fluorescent Probes and Chemicals, 5th Edition" (1992) Molecular Probes, pp. 90-93; hereinafter Haugland). Specifically, the Examiner contends that it would have been *prima facie* obvious to a skilled artisan to employ a peptide such as Crk-II and any fluorescent pair as taught in Haugland in the methods disclosed by Lee and Pollok for monitoring a post-translational modification enzyme activity. For the reasons stated hereinabove with respect to the rejections based on §102, the conclusion is inescapable that neither Lee nor Pollok provide response for all of the recitations of Applicants' claims. Indeed, neither Lee nor Pollok describe a peptide substrate that can monitor the effect of an enzyme on the substrate through changes in

conformation and concurrent changes in the distance between proximity sensors. Inasmuch as the prior art clearly fails to supply some motivation or incentive to one of ordinary skill in the art to arrive at the invention as claimed (In re Dow Chemical Company, 5 U.S.P.Q. 2d 1929 (Fed. Cir. 1988)), the rejection of claims 78-88 and 90-93 is untenable.

Accordingly, the rejection of claims 78-88 and 90-93 under 35 U.S.C. §103 based on the combined disclosure of U.S. Patent Nos. 6,410,255 and 5,795,729 considered in view of Haugland must be withdrawn.

CONCLUSION

As noted previously, U.S. Patent No. 6,376,257 was cited in the March 10, 2003 Official Action, but was not applied against any of the claims. That being the case, no detailed discussion of this reference would appear to be in order. *Oetiker v. Jurid Werke GMBH*, 215 U.S.P.Q. 21 (D.C. Cir. 1982). Suffice it to say that the U.S. Patent No. 6,376,257 fails to provide evidence of lack of novelty or obviousness with respect to the subject matter of the claimed invention.

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that all of the rejections set forth in the March 10, 2003 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

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